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Hereditary factor in allergy

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THE HEREDITARY FACTOR IN ALLERGY

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INTRODUCTION.

Heredity as an important factor in the etiology of allergic disease has long been accepted by investigators in the field of biologic sciences. As long ago as 1698 Sir John Floyer recognized this fact, when he wrote: "As my asthma was not hereditary from my ancestors, so, I thank God, neither of my two sons are inclined to it, who are now past the age in which it seized me." This pronouncement is certainly more than a careless, extemporaneous statement, and leads the investigator to surmise that the hereditary factor in the transmission of asthma had been under accusation even before this time.

With this as a beginning, however, investigators of many periods have made sporadic forays into the field of research to determine, if possible, just what part heredity plays in the etiology of hypersensitiveness, but not until the last quarter century, when the prevalence of allergic diseases has been more universally recognized, has this research yielded results that are convincing. Even yet, while the hereditary factor is quite generally accepted, its significance is discounted

by many observers, and the three-cornered battle still rages over the question of its hereditary aspect---whether it is in truth a definite character following the laws of Mendel, and if so, whether it is a dominant or a recessive character.

The problems that confront the investigator are legion. In the first place, allergic diseases appear to be primarily a condition found in the human species. Unfortunately, propagation of the human species is a slow and laborious process, as man measures time and effort; also, it is not a factor that can be controlled, or even supervised, by the investigator. Furthermore, the human species does not produce in litters---seldom in multiple births---and it is unthinkable that they can be made to produce offspring seasonally or with any regularity whatsoever. With this paucity of numbers of the issue on the family tree, scientific conclusions are impossible of accomplishment in the lifetime of one investigator, or one group of investigators. Since "one swallow does not make a summer," so also do a few isolated cases fall short of proving a scientific thesis.

As an introduction to this discussion it may be well to standardize the terminology, and thus avoid any misconstruction that too often characterizes any discussion of the subject.

Richet, in 1893, employed the term "anaphylaxis" as

meaning "without protection." "Allergy" is defined by Von Pirquet as "altered activity." Coca and Cooke used the term "atopy" as meaning "strange disease." Although the terms "allergy" and "atopy" may be used interchangeably, the word "anaphylaxis" indicates an acute condition, of sudden onset and often fatal termination, that may be produced in all mammals by foreign protein innoculation. Allergy and atopy, in the scope of this study, denote that condition of hypersensitiveness that is chargeable with the many chronic foreign-protein diseases.

The list of allergic diseases embraces many conditions of protein hypersensitiveness. The several investigators studied include the following, although no one investigator has included them all: Angioneurotic edema, asthma, atopic coryza, bronchial asthma, early hay fever, eczema, essential hypertension, gastroenteritis, late hay fever, migraine, and urticaria.

HISTORICAL.

Asthma is the oldest known of allergic diseases, and has been recognized for many years, but following the observation of Sir John Floyer, nearly a century passed before any other writings on the hereditary factor are prominent in the literature. Cullen, in his Practice of Medicine (1784), and Ryan (1793) both suggest the possibility of hereditary transmission. American authors, as Eberle (1831) and Goode (1836), maintained that hereditary transmission was the generally accepted opinion. Andral (1839) mentions heredity as one of the prime factors predisposing to asthma. Ramadge (1847) gives an instance in which the disease appeared in four generations. Salter (1860), in a study of 35 cases, determined a positive family history in 38 per cent. Steavenson (1879) described how he inherited his asthma from his paternal grandmother. Geddings (1883) states: "That this tendency is hereditary in nature is conceded by every prominent writer on asthma." Osler (1884) speaks of the hereditary tendency manifested in allergic dermatoses.

The first important contribution to this study in the present century is that of Czerny (1905), in discussing asthma and other allergies in his exudative diathesis. Drinkwater (1) in 1909 records a very im-

pressive family history. The more recent investigators and their conclusions have tended to corroborate these early observations.

Balyeat (8) believes the phenomenon follows Mendel's law as a single dominant character, for with bilateral family history, symptoms were manifested in the first decade in 58.6 per cent of cases; in the second decade in 10 per cent of cases, and after the age of 30 years, in only 0.3 per cent. With unilateral antecedent history, symptoms appeared in 32.3 per cent of cases in the first decade and in 30.8 per cent in the second decade.

Buchanan (2) says: "Transmission of migraine is the expression of the Mendelian phenomenon." He found that with unilateral family history in one hundred families, with 630 children, 22.6 per cent had migraine; in 17 families with no antecent history, out of 115 descendants 26 per cent had migraine; with bilateral history in three families, with 15 children, all had migraine.

Cooke (3) makes the unqualified statement that 7 per cent of the race is hypersensitive. With this remarkable incidence of the phenomenon, it is not to be wondered that Doctor Balyeat remarks: "There is a cause for the apparent overenthusiasm of physicians who deal in allergy as a specialty."

MENDEL'S LAW.

Mendel's law, or the mendelian hypothesis, enunciates the premise that the offspring is not intermediate in type between its parents, but that the type of one or the other parent is predominant. If two well-defined varieties of the same species be cross-fertilized, the resulting hybrid offspring will show the distinguishing characteristics of one parent only. This inherited characteristic he terms "dominant." The characteristic of the other parent, however, known as "recessive," is latent, and will appear in the next generation bred from the hybrid. The offspring of this second generation will be of two kinds, 75 per cent of the offspring having the dominant character and 25 per cent the recessive character. If these two recessive members of the third generation are bred together, the subsequent generations will show constantly the recessive character.

As regards the dominant members of the third generation, they divide themselves into two orders. One-third of these members produce purely dominant offspring; the other two-thirds are true hybrids, showing a mixed character, and each subsequent generation from them shows the same proportion of pure dominants, pure recessives, and hybrids. This law may be expressed by the formula, n(DD plus 2DR plus RR), in which DD represents pure domi-

nant offspring, RR pure recessive offspring, DR hybrid offspring, and n the number of the generation.

From this it is seen that "dominant" means the presence of a character, and recessive is the absence of the dominant character. Complex ratios, of course, appear through all lines of descent, due to differences in two or more allelomorphs. In the human species, where inbreeding is somewhat frowned upon, new characters of both dominants and recessives are introduced with each new generation to complicate the picture. In general, however, the segregation from the third generation (f-3) may be expressed as follows: DR⟶3DD:1R.

TABLE 1.---Mendelian Segregation of Offspring After Third Generation.

DD	DR	RR
1	2	1
3	2	3
7	2	7
15	2	15
31	2	31
2n − 1	2	2n − 1

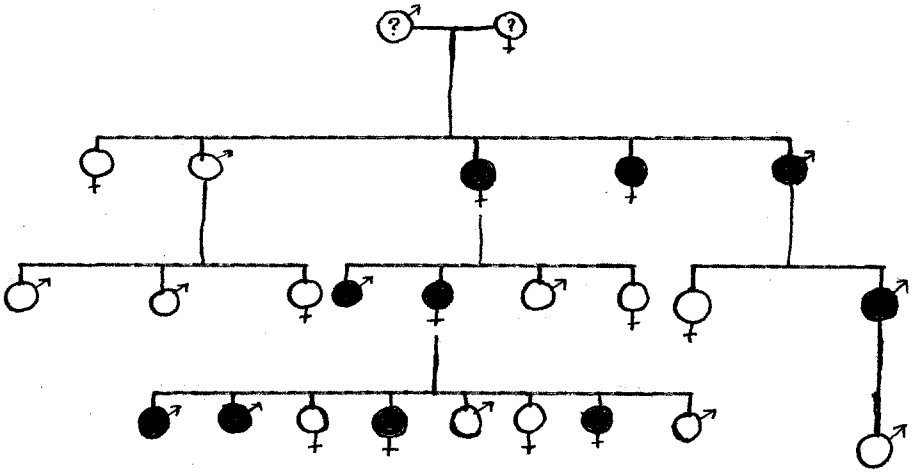
or

Gametes	D	D	x	R	R
Zygotes	D DD	D DR		R DR	R RR

OBSERVATIONS.

In a short study of the incidence of asthma in an allergic family by Drinkwater (1), made in 1909, a waning interest in the hereditary aspect of allergic disease received new impetus. In this study he found ten normal and ten sensitive individuals, the offspring of unilateral heritage. The first generation (f-1) shown in the chart below is assumed to be of unilateral sensitive antecedent, for Drinkwater observes; "For there was almost certain a heterozygous abnormal parent of those shown in the first line.

CHART I.---Incidence of Spasmodic Asthma.



● =Hypersensitive. ○ = Normal.

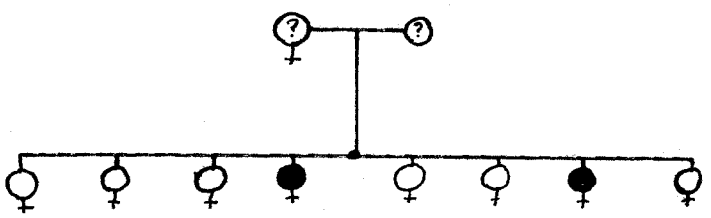
From this modest beginning, lamentably incomplete and unconvincing, proceeded the modern study of allergic phenomena, which now comprises a distinct specialty in

the study and practice of medicine and the biologic sciences. This particular observation marks the beginning of the present era of experiment and research, which is showing such a marked activity and remarkable progress.

Migraine was the next allergic manifestation to get into the literature, from the standpoint of hereditary transmission. Buchanan (2) made his study of 127 families, in which 198 individuals had migraine and 610 had the migraine character without definite symptoms. His work encompassed the mendelian character of transmission, and in substantiation of the growing belief of that time that allergy was a mendelian dominant, he observed that the offspring of unions where both parents had the pure migraine character---union of homozygotes ---100 per cent had migraine.

Segregation of the migraine character in families in which a person with migraine and a person without migraine have been crossed is shown in the following charts of Buchanan's:

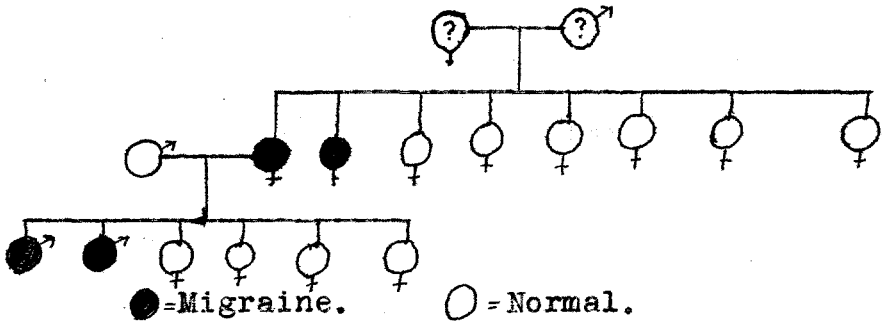
CHART II.---Unilateral Migraine Character.



The value of searching for all the evidence available in a family in which one member has migraine is dem-

onstrated in the next chart. Here it can be presumed that a parent in the first generation had migraine, or the migraine character, assuredly, because of the dis-

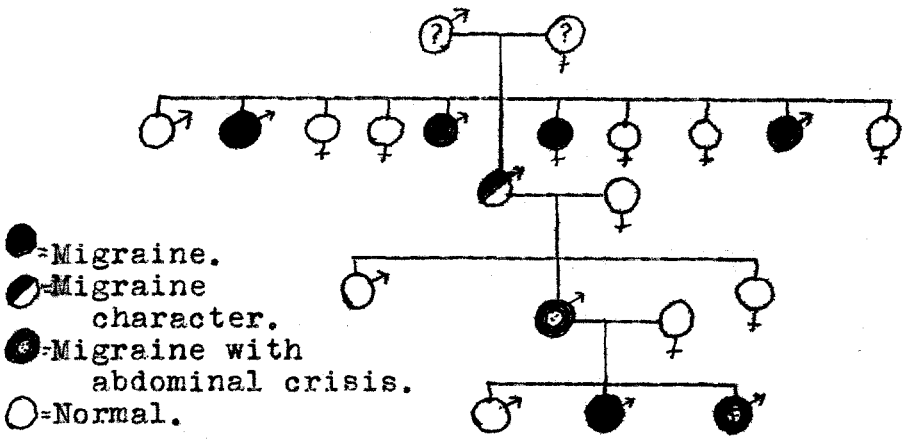
CHART III.---Segregation of Migraine in a Family of Unknown Heritage.



tribution in the second generation. The segregation is carried into the third generation.

Doctor Buchanan identifies migraine as an affection characterized by pain, vomiting, mental depression, visual phenomena, and many vague somatic symptoms, which usually disappear in the fourth decade. In his study he

CHART IV.---Migraine with Abdominal Crisis.

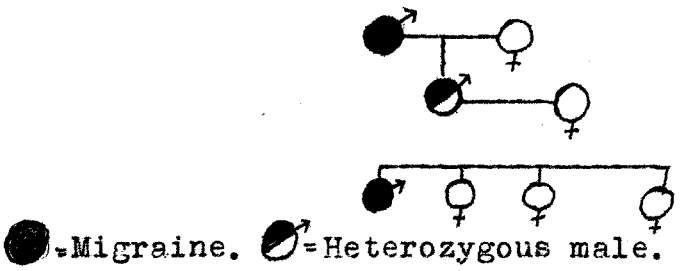


observed also the specificity of types of migraine, and this determination is shown in Chart IV for the transmission of migraine with abdominal crisis.

Doctor Buchanan experienced marked difficulty in working out the ratio, however, because of the difficulties of control and the lack of report from individuals who do not develop symptoms. Then, too, there is always to be considered the factor of exposure to the atopen, or the questionable cases, where the symptoms may be so mild as to attract no notice.

The heterozygous status of the male of the second generation is demonstrated in Chart V by the appearance

CHART V.---Heterozygous Transmission.



of the character in the final generation. This status is comparable to the migraine character without definite symptoms, and there may be no symptoms whatsoever, since there is doubtless a factor of mendelian heredity having reached the third or subsequent generation in the parent mating in this chart.

The increased atopic character as expressed by the earlier age of onset is shown in the study by Cooke and

Spain (3), whose work was a follow-up of that of Cooke and Vander Veer in 1916. These investigators, in a study of 462 clinical cases of allergic manifestations, determined a definite hereditary factor in hypersensitiveness. Of the number studies, 236, or 51.1 per cent, gave a history of unilateral antecedents and 34 cases, or 7.3 per cent, a bilateral antecedent history, making a total of 270 cases, or 58.4 per cent, giving definite antecedent history of hypersensitiveness. In contrast, only eight of 115 members from normal families---only 7 per cent---showed positive antecedent history.

As to age of onset, those offspring of negative antecedents manifested symptoms between the ages of 12 and 21 years, in contrast with a 53 per cent onset within

TABLE 2.---Comparison of Bilateral and Unilateral Antecedent History.

	Bilateral history.	Unilateral history.
Number of families.....	32	211
Total number of children.....	83	666
Number of atopic children.....	50	321
Average age of total children....	16.8	33.8

the first five years of life for those of bilateral antecedent history. For those of negative antecedent history, a maximum of 20 per cent manifested symptoms between the ages of 20 and 30, whilst the percentages of this late onset had dropped to 7 or 8 per cent for those of unilateral antecedents and only 4 per cent for those

of bilateral antecedent history. Furthermore, onset of symptoms after the age of 40 was negative in those individuals of positive antecedent history, whereas those from nonallergic families evidenced onset not infrequently at much later ages.

The data in Table 2 show with what painstaking care these investigators pursued their study. The average age of total children studied is seen to be considerably above the expected age of onset in the case of positive antecedent history; hence, the number of positive cases can be assumed to be quite complete for all cases that will manifest themselves among these individuals. The list of allergic diseases considered in this study is also quite complete, including all the accepted allergic affections with the exception of essential hypertension.

From this careful survey, Cooke and his associates were convinced that allergy is a mendelian dominant.

That allergy is of familial distribution was also determined by Abigail E. Smith (4) from an exhaustive study of a family through five generations, including 22 matings and 87 individuals. This investigator makes the further observation that given forms of allergic manifestations apparently tend to be prevalent among closely related individuals. Her study embraced asthma, hay fever, vasomotor rhinitis, urticaria, angioneurotic edema, and eczema, all of which diseases were prevalent in this

family. The study begins with a mating of two allergic individuals, but almost without exception the family accretions by marriage are nonallergic.

W. G. E., the son of first cousins (of unknown allergic history), married a first cousin of both parents. This fact, may it be noted, presents the so-called pernicious influence of inbreeding for perpetuation of family weaknesses. W. G. E., his wife, and one sister were all hypersensitive. Fourteen children came of this first mating, but nine of them died early, before the expected development of allergic disease, with no positive history. This study includes the remaining five children and their issue. The data in Table 3 beautifully demonstrates the ratio expected with allergy considered as a mendelian dominant character. The bilateral mating of the two allergic individuals gave 100 per cent hypersensitive issue, and the ratios throughout each succeeding generation follow closely the mendelian expectancy of a dominant character.

TABLE 3.---Numerical Summary of Cases and Analysis by Generations.

Generation.	Number of persons.	Positive.	Control.	Positive control.
P.	3	3	..	..
f-1.	5	5	5	0
f-2.	24	14	15	1
f-3.	28	12	3	0
f-4.	4	2	..	..
	64	36	23	1

TABLE 4.---Analysis of Cases According to Presence or Absence of Allergy in Parents.

Serial number of parents.	Children.	Positive	Per cent positive.
Bilateral inheritance.			
1 and 2	5	5	100
38 and 39	4	3	75
Unilateral inheritance.			
5	8	6	75
53	7	2	28
68	3	1	33
74	5	4	80
92	1	1	100
12	4	3	75
17	3	1	33
22	3	3	100
27	4	0	0
60	2	0	0
76	1	0	0
82	3	1	33
87	2	1	50
44	1	0	0
14	1	0	0
48	2	2	100
	50	25	50
Negative inheritance.			
79	1	0	0
35	1	0	0
	2	0	0

Although Buchanan (2) in 1923 failed to produce convincing evidence that asthma and "protein sensitivity" were dependent on a true hereditary factor, his findings appear insignificant when compared with those that Doctor Smith presents here. Buchanan's work in this instance included only 17 families with unilateral antecedent history, in which he found 102 negative and eight positive,

comparing with 36 families of negative antecedents, in which 226 were negative and 46 positive; seven families of unilateral antecedents, in which 36 were negative and

TABLE 5.---Analysis of Occurrence of Allergic Phenomena, by Generations.

Generation.	Asthma.	Hay fever.	Vasomotor rhinitis.	Urticaria.	Angioneurotic edema.	Eczema.
P.....	0	0	2	1	1	0
f-1.....	1	1	3	2	0	1
f-2.....	1	8	8	4	1	4
f-3.....	2	2	2	8	4	7
f-4.....	0	0	0	2	0	2
	4	11	15	17	6	14

two were positive; and 24 families of negative antecedent history in which 126 were negative and 28 were positive. Doctor Smith's conclusion , on the basis of her finding in this study, is that "only in a large number of offspring can close approximation of the 3:1 ratio be expected." This premise appears as the weakness in the

TABLE 6.---Mendelian Expectancy with "Allergy" as Dominant and Recessive.

	Dominant (per cent).	Recessive (per cent).
DDxDD.....	100	0
DDxDR.....	100	0
DDxRR.....	100	0
DRxDR.....	75	25
DRxRR.....	50	50
RRxRR.....	0	100

Buchanan's work. Some of the individuals carried as negative doubtless would have shown as positive on careful scrutiny of allergic diseases considered; also, some allergic manifestations that were not included in the study may have been elicited.

A comparison of Doctor Smith's findings in the E. family with those of the expected ratio of the mendelian inheritance is shown in Table 7. These findings are

TABLE 7.---Comparison of Findings in the E. Family with Mendel's Expected Ratios.

	Theoretically hypersensitive (per cent)	Actually hypersensitive (per cent)
With "Allergy" as a Dominant.		
DRxDR	75.0	88.8
DRxRR	50.0	50.0
RRxRR	0.0	0.0
With "Allergy" as a Recessive.		
RRxRR	100.0	88.8
RRxDR	50.0	50.0
DRxDR	25.0	0.0

quite convincing that the results of this survey are more nearly in correlation with the ratios of Mendel's dominant character.

The interpretation of these comparative tables brings the student in accord with Doctor Smith's summation:

1. Not all the children of bilateral allergic inheritance can be shown to be hypersensitive, as is necessary in case the character is recessive.

2. In order to have any hypersensitive children in the case of single inheritance, if the character is recessive, it is necessary that the nonallergic parent carry the recessive character for "hypersensitive." Therefore, every one of the eleven persons who married

TABLE 8.---Percentages of Positive Cases in Families Studied by Three Investigators.

	Double inheritance. (per cent)	Single inheritance. (per cent)	Negative inheritance. (per cent)
Drinkwater, 20 cases...	0.0	50.0	0.0
Cooke, 1,889 cases.....	69.4	58.0	41.1
E. family.....	88.8	50.0	0.0
Expected ratio, dom't..	100 or 75	50.0	0.0
Expected ratio, rec've.	100.0	50.0	25.0

allergic members of the E. family and had allergic offspring must have been of allergic families. Only two of them had family history of allergic disease, and only one of the two was allergic.

That the several shock organs of the body are subject to hereditary influence, resulting in allergic manifestations, is the thesis of Dr. A. F. Coca (5) , and that an allergic individual, under adequate conditions of contact with a respective allergin, may be destined to begin to exhibit a particular form of allergy at a certain age of life to a certain allergin or group of allergins.

Doctor Coca distinguishes particularly between allergy (or atopy) and anaphylaxis, designating the sensi-

tizing bodies of atopy as "atopic reagins," called also "atopens" or "allergins," in contradistinction to anaphylactic antibodies. His study concludes that most individuals are equally exposed to parental contact with protein antigens, and the difference in its individual result is ascribed to the difference in resistance of the various shock organs---nose, lungs, skin, liver, etc. His work confirms that of Doctor Cooke (3) and his associates, that allergy is an inherited affection. He points out further that in the blood of allergic individuals exhibiting a specific cutaneous reaction, sensitizing bodies are nearly always demonstrable; that a human individual who produces only anaphylactic antibodies to an antigen is not atopically sensitive to that antigen; and that the atopic reagins are incapable of conferring anaphylactic hypersensitiveness on the classical test animal, the guinea pig.

Some interesting work on the transfer of foreign protein antibodies from mother to fetus is contributed by Ratner, Jackson, and Gruehl (6), following the work of Rosenau and Anderson. While this work is primarily protein sensitization of anaphylaxis, it is interesting to observe that actual immunity to disease resulted in some instances. The most significant findings, however, are the differences in the phenomena of intrauterine transmission in ruminants and in man, rabbits and guinea pigs.

Hypersensitiveness to horse serum was produced in the offspring by innoculation of pregnant guinea pigs, but this condition was a transient one, with a gradual recession until by the seventy-third day it has disappeared. Two viewpoints are prevalent as to the mechanics of this phenomenon, the vitalists maintaining that the chorionic villi have a selective function, the mechanists that they serve only passively as a filter. Some authorities hold to the belief that there is no interchange of antibodies from maternal to fetal blood except through injury to the placenta. These investigators, however, take the opposite stand, maintaining that the process is physiologic rather than pathologic.

Supporting the viewpoint of these authors is the oft-observed phenomenon that infants show an inherent early resistance to diseases---particularly to those to which the mother is immune. Lerebouilet and Buechner observed a marked resistance to variola in infants whose mothers had the disease during pregnancy. Burckhardt, the authors report, carried the experiment further, establishing the fact that mothers vaccinated in the late months of pregnancy confer upon their offspring a similar immunity. Infants thus indirectly immunized showed without exception a definite resistance to the virus, exhibiting the immune reaction to vaccination on the first day after birth, whereas the controls from nonimmune mothers gave almost universal positive reactions.

The authors also report a titration of maternal blood and cord blood from immunized mothers, with the antibodies equal in 84 per cent of their cases.

Experiments with ruminants, however, were disappointing to adherents of this premise, for here it was found that offspring of goats had no inherited immunity to anthrax, although the mothers were innoculated. Similar findings obtained with cows and sheep. On the other hand, the feeding of colostrum proved to be the immunizing agency of the newborn. Withholding it even for 36 hours was sufficient to rob the newborn of its normal immunity. But the histological differences in the placental walls of ruminants and rodentia offered a likely explanation: The placenta of ruminants is three cell layers thick, while that of the rodentia, as well as of Homo sapiens, consists of but a single cell layer separating the maternal from the fetal blood.

From this study one is brought to the conclusion that the passage of heterologous substances through the placenta occurs in man and rodents; that the placenta of these species is permeable to antitoxins and other protein-sensitizing substances, but the placenta of ruminants is not; and that this difference in phenomena of permeability is explained largely by the difference in histologic structure of the placentae of the different species. It is also strongly suggested that the colostrum of ruminants exerts a benign influence on the resistance to disease

of the newborn.

A study similar to Ratner and his associates, and substantiating their findings, was made by Lewis and Loomis (7), in which they produced artificial immunity to sheep and beef corpuscles, to B. typhosus, to B. abortus (Bang), and to horse serum. Through their study of artificially sensitized guinea pigs they found that certain inbred families differed markedly in resistance to experimental tuberculosis. From this finding it was determined that variations in familial resistance must depend upon a varied inheritance factor. An immunity was established in 40 per cent of their animals, to which a tolerance of 7 per cent was traceable to extraneous factors, leaving more than 30 per cent chargeable solely to the inheritance factor. Their determination, therefore, in the basis of their belief that allergic irritability is one of several inheritable factors which form a partial basis for natural resistance to tuberculosis.

In a study of one thousand cases Ray M. Balyeat (8) found 58.6 per cent of them with bilateral inheritance to allergic disease, manifesting symptoms in the first decade, in contrast with 32.3 per cent of unilateral antecedents reacting similarly. Only three of these cases of bilateral heritage showed onset of the affection after the age of 30, whereas 30.8 per cent of those of unilateral history gave age of onset between 20 and 30 years, against 10 per cent of those with bilateral

antecedents. For this study, hay fever and asthma were considered, and it was found that 21 per cent were sensitive to more than one atopen.

Proceeding on the hypothesis that exposure to the atopen largely governs sensitivity, Doctor Balyeat found that 43 per cent of these individuals were sensitive to feathers, while only 2 per cent were sensitive to rabbit hair. This finding is in hearty accord with the earlier finding of Peshkin on one hundred asthmatic Jews---who use rabbit-hair pillows---wherein he found 49 per cent of them sensitive to rabbit hair and only a negligible percentage sensitive to feathers.

Doctor Balyeat pursued a further study on 1,117 normal university students, wherein he observed not only the hereditary factor of asthma, but also the relationship of allergic disease to intelligence. Of this number of normal individuals he found a history of 8.3 per cent with a history of asthma and hay fever among relatives of the first degree, against 60.1 per cent in patients suffering with hay fever and asthma. From this survey he is convinced that allergy is a single dominant character, on the mendelian hypothesis of inheritance.

This investigator made a further determination that migraine and eczema are interchangeable with asthma and hay fever, which substantiates the general modern belief that inherited allergic tendency is a general condition rather than one of specificity, producing a definite

disease entity in each succeeding generation---that the asthmatic parent may produce offspring that will manifest hay fever or some other allergic disease as a result of its inherited tendency.

Doctor Balyeat's findings on the intelligence factor, from a study of 40 allergic and 40 nonallergic students, is here presented in Table 9.

TABLE 9.---Summary of Intelligence Quotient in Relation to Allergic Disease.

	Allergic.	Nonallergic.
Below normal---		
Number of students	0	0
Per cent of total	0	0
Normal---		
Number of students	12	32
Per cent of total	30.0	80.0
Superior---		
Number of students	12	4
Per cent of total	30.0	10.0
Very superior---		
Number of students	15	2
Per cent of total	37.5	5.0
Near genius---		
Number of students	1	0
Per cent of total	2.5	0.0

Doctor Balyeat's conclusions are so lucid and so germaine that the writer takes the liberty of presenting them here:

1. Inheritance appears to be the chief factor in determining whether an individual will ever develop hay fever of asthma, and to some extent governs the time of life when symptoms will appear.

2. The earlier in life an individual becomes sensitive, the greater the tendency to develop a sensitivity to more than one group of atopens.

2. The extent to which an individual is exposed to

to any given protein has much to do with determining whether a sensitivity to that particular protein will develop.

4. The substance to which patients become specifically sensitive, chemically and clinically, in many cases is a nonnitrogenous one.

5. Clinically, the substance, whether protein or nonprotein, to which a patient becomes specifically sensitive may be found in cow's milk and breast milk.

6. A child may be born specifically sensitive to a food protein or a substance closely allied with it.

7. The ability to become sensitive is transmitted from one generation to another, but not the specific state.

8. The character of the inheritance is as a single dominant.

9. It appears that the linkage eczema and migraine are interchangeable with hay fever and asthma.

10. Allergic patients develop general resistance to infectious disease far above normal.

11. A careful, detailed history will usually determine whether an asthma or hay-fever patient has complications that need investigation other than tests for specific sensitivity.

12. Allergic patients whose symptoms manifest themselves within the first decade seldom develop tuberculosis.

13. Hay fever and asthma are comparatively absent in the insane.

14. From our findings it appears that allergic students may be far above the normal in intelligence.

15. There is a cause for the apparent overenthusiasm of physicians who deal in allergy as a specialty.

That puberty exerts a significant change in the allergic manifestation is the finding of George W. Bray (9) after his study of two hundred consecutive cases in the Hospital for Sick Children, London. Asthma, hay fever, eczema, urticaria and migraine were the allergies to which this study was devoted. He made the further observation that transmission appears to be twice as frequent through the female as through the male, for whilst the history is twice as frequent on the mother's side, when the parents are unaffected the transmitter is again twice as frequently

the mother. When the male is unaffected and the female has allergic disease or the allergic character, twice as many children are affected with allergic diseases as when the

TABLE 10.---Relationship Between Age and Family History in Allergic Disease.

Age at onset (years).	Unilateral.		Bilateral.		Negative.		Grand total.		
	M.	F.	M.	F.	M.	F.	M.	F.	Total.
0-1	20	3	4	3	11	3	35	9	44
1-2	12	5	8	2	5	5	25	12	37
2-3	10	6	3	2	6	1	19	9	28
3-4	11	3	2	2	7	1	20	6	26
4-5	10	2	3	1	4	4	17	7	24
5-6	5	4	2	1	5	..	12	5	17
6-7	6	1	..	..	1	..	9	2	11
7-8	3	1	..	1	1	..	4	2	6
8-9	...	...	..	..	1	2	1	2	3
9-10	1	..	..	..	1	..	2	..	2
10-11	...	..	..	..	1	1	1	1	2
	78	25	22	12	45	18	145	55	200

male is affected and the female is not. Doctor Bray finds that a positive family history of allergy is elicited in about 70 oer cent of the cases of asthma in children. More than 50 per cent of the cases give a unilateral history and less than 20 per cent give a bilateral history. About 10 per cent appears to be the maximum of incidence in families of presumably nonallergic individuals.

For the purpose of this study, late cases and cases of a known extraneous etiology were excluded, to give a clear record of the hereditary transmission of the disease. In all, 4,152 relatives were reported on, or an average of

more than 20 per patient. Since this study was confined to patients in a children's hospital, necessarily all of them had developed within the first decade of life. The relationship between age and family history is shown in

TABLE 11.--Relationship of Sex Incidence.

	Males.		Females.		Total.	
	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.
Total cases....	145	72.5	55	27.5	200	100.0
Family history-						
Unilateral...	78	75.7	25	24.3	103	51.5
Mother.....	48	73.0	18	27.0	65	64.0
Father.....	30	81.0	7	19.0	37	36.0
Bilateral....	22	64.7	12	35.3	34	17.0
Negative.....	45	71.4	18	28.6	63	31.5
Total Related Persons.						
Affected.....	342	57.3	255	42.7	597	14.3
Unaffected...	1,712	50.9	1,650	49.1	3,362	81.0
Transmitter..	64	33.2	129	66.8	193	4.7
Individual Diseases.						
Asthma.....	278	63.5	160	36.5	438	73.3
Hay fever.....	17	46.0	20	54.0	37	6.2
Eczema.....	92	63.4	53	36.6	145	24.3
Urticaria.....	51	68.9	23	31.1	74	12.4
Migraine.....	13	27.0	35	73.0	48	8.0

Table 10. Table 11 shows the relationship of sex incidence, in which the preponderance of transmission through the female is shown to be 1.6:1.

Positive family history is here shown to be definitely established in 68.5 per cent of the cases studied, in which 51.5 per cent is of unilateral antecedent and 17 per

cent bilateral; but negative history elicited may be in fact positive antecedent, for the allergic diathesis may have come through the preceding generations unnoticed, and

TABLE 12.--The Inheritance Factor.

Father..... A Mother..... A	A T	A U	T U	T A	U A	U T	T T	Total.
Number of families 7	4	14	21	8	21	45	17	137
Number affected...43	32	56	54	43	87	133	79	527
Transmitters..... 6	12	5	30	13	8	70	49	193
Unaffected.....51	38	75	170	68	118	314	149	983

A--Affected. T--Transmitter. U--Unaffected.

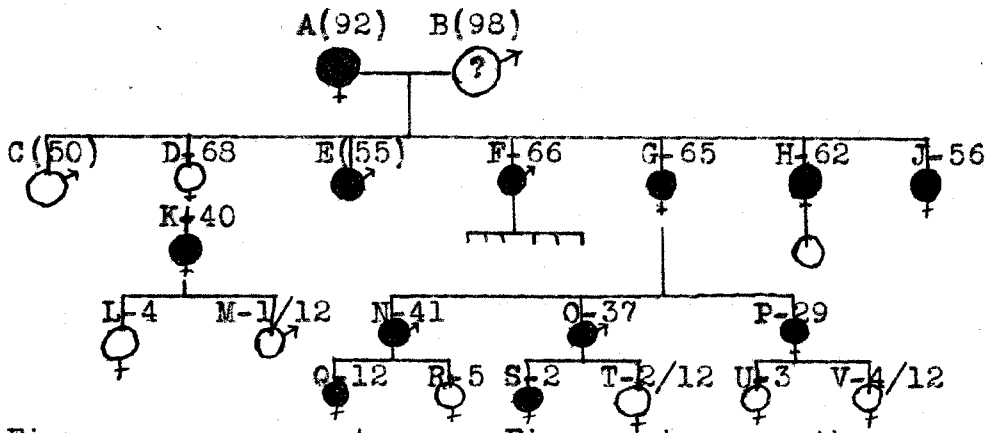
have resulted in transmission through a parent with the allergic character. The author quotes Adam as saying: "Asthma is no more hereditary than phthisis of gout; the tendency---the soil---is inherited; whether or not the disease will develop depends on nature."

The facts established are that the allergic diathesis is transmitted as a mendelian dominant; that the greater the heredity, the earlier are symptoms manifested; that the earlier in life the individual becomes sensitive, the greater the tendency to multiple sensitization; that hay fever, asthma, eczema, urticaria, angioneurotic edema and migraine appear to be intimately correlated and to be interchangeable; that a child born in a family with pure hay-fever lineage is much more likely to be affected with hay fever than with asthma, for example, and that this same

rule obtains with other allergic manifestations; and that where several members of one family are affected, sensitization is not identical as regards the specific proteins, nor are the clinical types of allergy or the symptoms displayed in each type themselves identical in different members of the same family.

Allergy is the most important biological and medical problem that exists, in the opinion of Frank L. Apperly (10). This author makes a fine distinction between the phenomena

CHART VI.---Inheritance from One Allergic Parent and One of Suspected Allergic Diathesis.



Figures are present age. Figures in parentheses are age at death. A-Hunger pains and sinking feeling. B-Eczema. E-Infantile eczema. F-Hyperacidity symptoms. G-Migraine, hunger pains, hypertonic stomach. H-Infantile eczema. J-Hunger pains and sinking feeling. K-Hay fever. N-Hay fever and hypertonic stomach. O-Infantile eczema, asthma and pruritis. P-Pruritis. Q-Infantile eczema. S-Infantile eczema.

of anaphylaxis and allergy. Inheritance, he believes, is the chief factor, though too frequently unrecognized by the medical profession.

Doctor Apperly's study included five generations of one family, for in the lineage shown in Chart VI, the parents of A are known to be hypersensitive. In the case of B, however, there is no definite history, but the incidence of allergy suggests that he might carry an allergic diathesis. No influx of allergic blood by marriage can be estabiiehed with the possible exception of B.

An interesting observation by this author is the Iongevity of allergic families. He also notes a remarkable resistance to infection, particularly to tuberculosis.

J. A. Kolmer (11) expresses doubt that a child is actually born with an allergic state, but rather that he acquires it during early childhood, particularly to horse serum and other sera. This phenomenon, he avers, accounts for the sudden and tragic deaths in children receiving their first antitoxin injections, which he terms "natural allergy." On the premise that the parents are known sometimes to have a sensitization to the particular serum to which the child reacts, he argues that the inheritable factor is merely an increased capacity for allergy antibody formation, the mechanism of which is unknown.

From the standpoint of this study, Doctor Kolmer is referring to the phenomenon of anaphylactic shock, and he draws a comparison between this and the phenomenon of allergic disease that is untenable,, considering the findings of other authors quoted herein.

Doctor Kolmer has observed that the phenomenon is

a vasodilation mechanism in anaphylaxis. Since epinephrine corrects the condition, paralysis of the muscles of the blood vessels is the theory he advances.

R. S. Alvarez (12) calls attention to the fact that Jenner, in 1798, noted the wheal formation, with resultant erythema, following in 18 to 24 hours after vaccination of an immune person, which he termed the "immune reaction." She discusses at length the acute allergic reaction, which this survey considers the anaphylactic phenomenon, wherein the symptoms are sudden, acute, and not infrequently fatal. The chronic allergy she treats as of unknown origin---possibly inherited.

A challenge to the modern theory of allergy is offered by Sterling (13) in his study of work being done in European clinics, where the treatment appears to be entirely symptomatic, and not attended by the desensitizing efforts of modern therapeusis.

Experimental transmission of hypersensitiveness from mother to child in human beings by Bell and Erikson (14) resulted in 100 per cent transfer. Their studies are of considerable importance for their work in determining the similarities and differences of hypersensitiveness and anaphylaxis, which they, too, consider as similar phenomena but of different significance. The permeability of the human placenta to various immune bodies is definitely established by their work. Diphtheria antitoxin

has been found by many investigators to be transmissible, but these workers were successful in effecting the transfer of tetanus toxoid, the complement-fixing bodies of tuberculosis, and bacteriolysins. They found convincing experimental evidence that the transfer is made from fetus to mother as well as from mother to fetus.

Employing the Prausnitz-Kuestner method, they studied the offspring of five cases of hay fever and five of asthma in detail, and their work resulted in the transmission of skin sensitization in 85 per cent of human beings. The blood was obtained from the mother and from the newborn child by venipuncture, defibrinated, centrifuged, and the serum sterilized by passing through a Seitz filter. One-tenth cubic centimeter of each serum was injected intracutaneously into two normal individuals for controls. The transfer was found to be sufficient to give positive reaction in dilution as high as 1:320 in one case.

Cord blood and whole blood from the infants was also used, but gave negative results in all cases. The experiment also was made both before and after the feeding of colostrum to the infants, to determine the influence of this substance to carry over immune bodies from mother to offspring. With the known beneficent effect of colostrum feeding in ruminants, this particular feature assumes a fine significance.

The results of the injections of the mother's serum

TABLE 13.---Bell and Erikson's Results.

Disease.	xMother sensitive to	zReading of direct test.	Transfer made to nonrelatives.	Effective serum dilution.
1. Hay fever	Timothy 0.001	Moderate	Slight	1:20
	Ragweed 0.001	Marked	Moderate	1:40
2. Hay fever	Ragweed 0.001	Marked	Moderate	1:160
3. Hay fever	Timothy 0.001	Marked	Marked	1:160
	Ragweed 0.001	Marked	Marked	1:320
	Orange 0.9	Marked	Slight	Undiluted
	Spinach 0.9	Marked	Marked	Undiluted
4. Hay fever	Ragweed 0.01	Marked	Marked	Undiluted
5. Hay fever	Timothy 0.001	Marked	Marked	1:160
6. Asthma	Feathers 0.1	Marked	Marked	1:80
	Goose epithelium 0.01	Moderate	Moderate	1:40
	Goat epithelium 0.01	Marked	Marked	1:80
7. Asthma	Fish glue 0.001	Marked	Marked	1:40
	Large variety of fish	Marked	Marked	1:40
8. Asthma	Goat epithelium 0.1	Moderate	Moderate	1:40
9. Asthma	Feathers 0.1	Moderate	Moderate	1:40
	Chicken epithelium 0.1	Moderate	Moderate	1:40
10. Asthma	Goat epithelium 0.1	Moderate	Moderate	1:20

xStrength of solution determined in milligrams of nitrogen per cubic centimeter.

zMarked reactions were those showing a wheal at least 1.5 centimeters in diameter with an irregular margin; moderate reactions, those measuring less than 1.5 centimeters and more than 1 centimeter in diameter with an irregular margin; slight reaction, less than 1 centimeter in diameter but greater than control.

were positive in all ten cases, dilutions varying from 1:40 to as high as 1:320, as shown in Table 13.

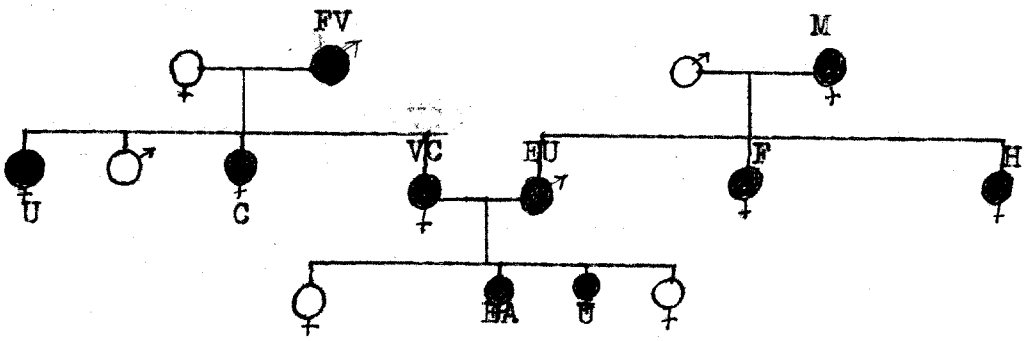
An illuminating case is cited by Oriel(15) of a boy of 19 suffering with eczema. He was found to be sensitive to eggs, fish and wheat. Investigation disclosed the fact that the father also was sensitive to these proteins, and had suffered with asthma in early life. Serum of this egg-sensitive patient was found to produce a wheal within 24 hours after injection into a normal person and the subsequent ingestion of egg by the normal person.

This phenomenon was noted particularly on individuals with hypochlorhydria and achlorhydria, but in no case on a person with hyperchlorhydria. Thus, this author adds a new observation to the field of allergy, and provokes the speculation of the effect of the acid secretion of the stomach on hypersensitiveness.

Hyperirritability of the vagus, or autonomic system, is the contribution of Warren T, Vaughan (17) as a result of his exhaustive study. This phenomenon was noted most particularly in asthma and urticaria, and the author suggests the likelihood that domestic irritation may be an important factor in provoking the onset of allergic disease. Irritability is usually a positive finding in allergic individuals, and this writer suggests that the whiny, irritable child may be manifesting a mild reaction to an allergic disease.

Doctor Vaughan found that 50 per cent of the descendants of one allergic patient showed evidence of hypersensitiveness at some time during life. With bilateral allergic parentage probably more than 50 per cent will manifest sensitivity---most certainly, he believes, it will appear at an earlier age. The symptoms may skip a generation, the allergic character being carried nevertheless as a mendelian dominant, opening again the question of expo-sure.

CHART VII.---Heredity and Pleotropism of Allergy.



F-Food upset. V-Vasomotor rhinitis. U-Urticaria. A-Asthma. C-Colitis. M-Migraine. E-Eczema. H-Hay fever.

The sensitizing proteins included clam, daisy, rose, quinine, milk, peach, almond, ragweed, chocolate, feathers, wheat, and strawberries. Two were sensitive to strawberries, and two to ragweed, but otherwise no two individuals had the same reaction. Of the two sensitive to strawberries, one was sensitive to this protein alone, whereas the other was sensitive also to feathers and wheat. Of the two sensitive to ragweed, one was sensitive to this alone and the

other to peach and almond in addition.

Doctor Vaughan also advances the thesis of inadequate defense of the allergic shock organs as a contributing factor to allergic manifestations, with which premise other investigators are in hearty accord.

Dr. William Lintz (16) opens a new field of speculation in his finding of allergic disease in more than 50 per cent of his cases of essential hypertension. This study includes a survey of three hundred cases. He finds many cases of allergic disease in the offspring of hypertension patients. His theory of allergic symptoms is in accord with that of Vaughan (17), that the manifestation is due to a disturbance of the vegetative nervous system.

In his study he finds small lungs a physical phenomenon associated with the majority of cases of hypertension. This character is doubtless inheritable, he maintains, and it is significant that the lungs are allergic shock organs.

The writer offers the observation in his own family of allergic disease running through four generations. Migraine in his maternal grandfather manifested itself in one daughter, who was the eldest of eight children. A brother of the writer's father developed eczema, but at a late age, and doubtless not of hereditary character. The writer's generation showed allergic disease in four of eight children, and he has one daughter who suffered with asthma at the age of 4 years, which dis-

appeared after a much-needed tonsillectomy. This child is now 10 years old, and since that time has manifested no symptoms of allergic disease. In the writer's generation the allergic diseases are eczema and migraine.

SUMMARY.

1. This study is a review of the writings of 17 investigators, studying approximately ten thousand cases, the majority of which were clinical cases of allergic disease.

2. In addition to the clinical cases, a number of reports on the experimental sensitization of laboratory animals are presented, representing exhaustive research into the phenomena of transmission of protein sensitivity.

3. Of the cases studied, approximately 57 per cent of them showed allergic disease directly traceable to an inherited, or at least a familial, tendency.

4. Allergy and anaphylaxis, while similar in mechanism, are different in clinical manifestation, the former being of a chronic nature, the latter acute, of sudden onset, frequently of fatal outcome, and capable of artificial production in a normal individual.

5. The field of allergic disease is a challenge to modern medicine and biological science that justifies diligent research and experimentation.

CONCLUSIONS.

1. The hereditary factor in allergic diseases is established beyond any reasonable doubt, appearing to be a mendelian dominant character.

2. Allergic disease appears to be confined largely to the human species, probably because of their cloistered existence and diet and habits of too refined a character.

3. Experimental work in allergic diseases is greatly hampered by the investigator's inability to control the mating of individuals and collect all the data necessary to a complete study. The slow rate of propagation of the species is also a stumbling block in the way of the investigator.

4. Exposure to a particular allergin is an important factor in the development of symptoms.

5. Insufficient resistance of the allergic shock organs may be the inherited trait that determines whether or not symptoms will develop.

6. Transmission of the allergic diathesis is general in character, and not of a specific nature as to the particular manifestation that will appear.

7. Offspring of allergic parents will develop symptoms at an earlier average age than those of nonallergic antecedents.

8. The earlier in life allergic symptoms develop, the more susceptible is that individual to multiple sensitization.

9. Longevity and increased resistance to infectious disease, particularly to tuberculosis, is a noticeable character of allergic individuals.

10. The allergic individual may be far above the normal in intelligence.

11. The interchange of allergic antibodies occurs during intrauterine life in man and rodentia, but appears to be a phenomenon of colostrum ingestion in ruminants, who confer no protein antibodies during pregnancy. This fact is logically adduced by the differences in histological structure of the placental walls of the different species.

12. There is justifiable cause for the apparent overenthusiasm of physicians who deal in allergy as a specialty, since approximately 7 per cent of the population is subject to allergic diseases.

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